Description

Mini-basket for analyzing active substance release from a medicament form

The following describes a device for analyzing in vitro active substance release from a solid medicament form, ~~consisting of~~ including a novel mini-basket, and the use of ~~said~~ the device.

During the development of a medicament form, the quality, efficacy and safety of the drug are tested inter alia by in vivo and in vitro analyses. The in vitro analyses are of particular importance as they are often able to demonstrate small changes in the medicament form which could affect its efficacy and tolerability (and thus the drug safety). By means of in vitro release analyses, the pharmaceutical formulation can be optimized while minimizing cost-intensive and time-consuming in vivo studies, and the quality of the manufactured batches can be monitored during development, storage and production (notes to DAB 1996, V.5.4. Active substance release from solid oral medicament forms, Govi-Verlag, published by Hartke, Hartke, Mutschler, Rücker, Wichtl). Comparing in vitro data results with in vivo studies can reduce the number of tests carried out on humans and animals, since conclusions can be drawn concerning the in vivo results in later samples.

An important condition for active substance absorption, and thus for bioavailability, is the active substance release from the medicament form (notes to DAB 1996, V.5.4. Active substance release from solid oral medicament forms, Govi-Verlag, published by Hartke, Hartke, Mutschler, Rücker, Wichtl). The pharmacopeias describe for this purpose a number of official in vitro release analysis methods with the known apparatuses associated with these methods. Thus, to determine the release of active substances from solid medicament forms such as tablets, capsules, pellets or suppositories, use is made of paddle agitators, rotating baskets and continuous flow cells. The first of these are closed systems in which the medicament form to be tested is located either in the cylindrical vessel belonging to the apparatus or in the rotating basket itself, and the paddle agitator and rotating basket serve for agitation. The continuous flow cell apparatus can be used as a closed system (return of the release medium) or as an open system (delivery of fresh release medium). Test liquid is

removed at set times and the medicament which has dissolved in it is measured. These apparatuses, paddle agitator apparatus, rotating basket apparatus and continuous flow cell, are known from European Pharmacopeia 1997, Govi-Verlag, pages 136 through 139, or from the US Pharmacopeia, The United States Pharmacopoeial Convention Inc., Twinbrook Parkway, Rockville, MD, pages 1791 through 1799 (USP 23/NF 18).

Medicament forms with modified active substance release include coated or uncoated medicament forms in which the rate of release or the site of release is deliberately changed. In addition, there are enteric-coated medicament forms which are resistant in the gastric juice and release the active substance in the intestinal juice. If the active substance is readily soluble in the release medium, these medicament forms can be tested with the aforementioned apparatuses (paddle agitator apparatus and rotating basket apparatus) after appropriate validation. In some cases the continuous flow cell is also used, especially if release profiles are to be recorded. The so-called sink conditions should be maintained during testing, i.e. the concentration of the active substance to be tested in the release medium should not exceed 30% of the saturation concentration.

In contrast to the observations made above, the analysis of in vitro active substance release from medicament forms with medicament substances which are sparingly soluble in the release medium can be problematic in the known paddle agitator and rotating basket apparatuses since, because of the limited volume, the release can be controlled by the solubility of the active substance and not by the delivery from the medicament form. In this case, the known continuous flow cell (as open system) can be of help since it continuously delivers fresh release medium. If the medicament form containing the sparingly soluble active substance is not enteric-coated, the use of the continuous flow cell is a suitable method for indicating the release profiles of medicament forms with modified active substance release. However, in the case of enteric-coated medicament forms, the integrity of the coating must be tested before the actual test of active substance release, i.e. the latter is preceded by an analysis step in an acid release medium. Should the analysis be carried out with the continuous flow cell, a pH gradient may develop in the first collected fractions, and this can falsify the results.

An enteric-coated medicament form can, for example, be a capsule containing the active substance enclosed in so-called pellets. These pellets can be enteric-coated, i.e. they are intended to release the active substance only at higher pH values, such as those obtained during passage through the intestinal tract. Consequently, these pellets become less and less stable as pH values increase, i.e. they release the active substance relatively rapidly in release media with higher pH values. In some circumstances it is no longer possible to differentiate between smaller formulation differences. If at the same time the active substance is only sparingly soluble in media with lower pH values, the result in this case does not point to the release from the medicament form, but instead is controlled by the solubility of the active substance. Although a release medium with a high pH value can obviate this, it cannot however be used on account of the aforementioned difficulty (poor differentiation).

A release medium with a moderate pH value, used in the known continuous flow cell apparatus, can on the one hand discriminate between different formulations and, on the other hand, can permit a release analysis by means of delivering fresh medium to avoid the solubility problems. A method is known from DE 29 42 129 A1 in which the dissolver chambers of at least two continuous flow cells are connected to each other. The aim of this is to ensure a controlled passage of dissolving medium with medicament particles or medicament forms from one cell to the next. In this particular case, however, it has been found to be difficult to analyze the resistance to gastric juice. On account of the pH gradient in the first basic fraction following previous use of an acid medium (acid residue liquid is necessarily still present in the hose system of the apparatus), the active substance precipitates and cannot be completely analyzed.

The object of the invention is therefore to develop a device for analyzing in vitro active substance release, with which device these disadvantages are eliminated.

The subject of the invention is a device for in vitro active substance release from a solid medicament form, ~~consisting of~~ including a mini-basket, characterized in that the bottom part (mini-basket) and the top part (lid) of the mini-basket are made of wire screen fabric, and the top part (lid) has a handle on the outer side.

Analyses are carried out on solid medicament forms, for example tablets, capsules, pellets, suppositories, or preferably enteric-coated medicament forms. The inside of the lid is secured with frictional engagement on the upper side of the mini-basket by means of one or more, preferably one to three, fixing clips, ~~particularly~~ more preferably one fixing clip, or other fixing devices, among other reasons so that the mini-basket can be fitted flush into the known continuous flow cells (type A and type B) (see European Pharmacopeia 1997, Govi-Verlag, pages 136 – 139, and also other pharmacopeias). The fixing clip is arranged, e.g. welded, centrally on the inside of the lid for example, without reducing the size of the wire screen fabric. Other fixing clips made of metal are also possible, for example arranged on the edge of the lid, or fixing clips without central section. The mini-basket of welded wire screen fabric is shaped as a cylinder whose upper and lower edges are enclosed by a narrow metal band. The wire screen fabric, ~~which consists for example of stainless steel~~ which can be made, for example, of stainless steel, can also be coated with a suitable material (e.g. gold), depending on the test liquid, in order to ensure that these parts do not react with the formulation being tested or with the test liquid or influence the response. The wire screen fabric can run in any desired direction, i.e. vertically/horizontally or also diagonally, but preferably vertically/ horizontally.

The dimensions of the mini-basket can vary depending on the in vitro release analysis which has been chosen. The following are approximate values. The height can in general be freely chosen, and depending on the continuous flow cell the maximum height of the mini-basket is 35 or 50 mm. Thus, for example, baskets can be used having a height of L (total height) = 10 mm to 40 mm, preferably = 20 mm, L_1 (height of the wire screen fabric) preferably = 16 mm, L_2 (height of the top metal band) preferably = 1 mm, L_3 (height of the bottom metal band) preferably = 3 mm, and a diameter of D (total diameter of the base) = 11.5 mm to 22.6 mm, preferably 11.9 mm (continuous flow cell type B) and 22.5 mm (continuous flow cell type A), particularly preferably = 22.5 mm (i.e. flush with the diameter of the chosen continuous flow cell), D_1 (diameter of the wire screen fabric) preferably = 16.5 mm, D_2 (diameter/width of the metal band) preferably = 3 mm, and lid whose diameter corresponds to that of the mini-basket and whose height corresponds to the width of the metal band L_3 (height of the metal band) preferably = 3 mm. The size and the material of the handle can vary, but complies with that of the mini-basket. The design of the handle is such that the mini-basket can be easily removed from the

in vitro active substance release apparatus. A bracket, stirrup, knob, rod or eyelet can be used, for example, or a combination of rod and eyelet is conceivable, but a bracket is preferable. The attachment of the handle on the lid, centrally or at the lid edge (metal band), should be done as far as possible without reducing the size of the wire screen fabric surface. The handle can for example be welded, screwed or riveted onto the lid, the latter attachment forms can also include the fixing clip.

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An illustrative embodiment of the invention is represented in ~~Figure~~ Fig 1 and is explained in greater detail below:

The mini-basket (1), whose dimensions are preferably chosen (see last but one paragraph) such that it can be introduced flush into the appropriate apparatuses depending on the in vitro release analysis to be carried out (e.g. paddle agitator and/or continuous flow cells type A or type B), A ~~consists of~~ includes a bottom part (mini-basket) (2) and of a top part (lid) (3) whose dimensions are determined by the chosen in vitro release method(s) and the associated size(s) of the apparatuses. The mini-basket (2) is made of welded wire screen fabric and is cylindrical in shape. The wire thickness of the wire screen fabric (d) can be from 0.1 to 0.3 mm for example, preferably from 0.2 to 0.3 mm and particularly preferably 0.254 mm. The clear mesh width can be chosen, depending on the medicament form to be analyzed, to be from 0.1 mm up to the diameter of the particle to be analyzed, preferably from 0.2 to 1 mm, particularly preferably 0.55 mm. The top edge and bottom edge of the mini-basket (2), the edge of the lid (3) and the edges of the base plate of the mini-basket and the upper face of the lid are enclosed by a narrow metal band (4), preferably of the same material as the wire screen fabric. The edge of the lid (3) ends flush with the upper edge of the mini-basket (2). In addition, lid (3) and mini-basket (2) are held together frictionally by a fixing clip (6) which inter alia can have A the width of the metal band, without ~~said~~ the fixing clip (6) reducing the size of A the wire screen fabric. The lid (3) is provided with a bracket (5) handle, e.g. of the same material. The bracket is used for lifting the mini-basket out of the in vitro active substance release apparatus. The dimensions of the bracket secured on the lid or also of the other handles can vary, preference being given to a height of 4 mm and a width of 2 mm in the case of the bracket.

The subject of the invention is also a method for in vitro active substance release from a solid medicament form (e.g. tablets, capsules, pellets),

preferably enteric-coated pellets, by testing in acid release medium and subsequently at a higher pH, which method is characterized in that a mini-basket as described above, containing the solid medicament form, is placed in a vessel of a known paddle agitator, the integrity of the coating is tested in the acid release medium, the mini-basket is then lifted out of the vessel of the known paddle agitator with the aid of the handle located on the lid, and it is introduced into a known continuous flow cell, and the release of the active substance from the medicament form is tested at a higher pH. The mini-basket is constructed such that it fits flush into the cell and the test medium can flow through the meshes.

A further embodiment of the mini-basket (shown in Fig. 8) differs in that it has a top part (lid) (3) modified to the dimensions of the mini-basket (2) and in the form of a plate to which a rod (5) is secured (e.g. welded) and which has one or more, preferably one to three, fixing clips (6) which hold the mini-basket securely and permit a rotation concentric to the axis of the mini-basket, comparable with the rotating basket apparatus described in European Pharmacopeia 1997, Govi-Verlag, page 137. Except for the lid, the novel mini-basket corresponds to the description given above. An operation similar to the known rotating basket apparatus is therefore possible.

A subject of the invention is therefore a method for in vitro active substance release from a solid medicament form by testing in acid release medium and subsequently at a higher pH, characterized in that a mini-basket with rod, as described in the previous paragraph, containing the solid medicament form is placed in a vessel of a known rotating basket apparatus and the integrity of the coating is tested in the acid release medium, after which the mini-basket is lifted out of the vessel of the rotating basket apparatus, the lid in the form of a plate with rod is replaced by a corresponding wire screen fabric lid with handle, as described above, and introduced into a known continuous flow cell with the aid of the handle, and the release of the active substance from the medicament form is tested at a higher pH. The medicament form to be analyzed can therefore likewise be analyzed in the rotating basket apparatus and then in the continuous flow cell.

Using the mini-basket, it is therefore possible to exploit the advantages of different systems for testing the in vitro active substance release from complicated solid oral medicament forms. The active substance release

can be performed in one analysis operation, the results of which can improve drug safety.